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John A. Chiorini

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NATIONAL INSTITUTE OF HEALTH
C/O Ballard Spahr Andrews & Ingersoll, LLP
SUITE 1000
999 PEACHTREE STREET
ATLANTA, GA 30309

EXAMINER

BURKHART, MICHAEL D

ART UNIT

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1633

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/719,311	Applicant(s) CHIORINI ET AL.	
	Examiner MICHAEL BURKHART	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 September 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2,3,6-28,30-36 and 38-45 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2,3,6-28,30-36 and 38-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/29/2008 has been entered.

Claim Objections

Claims 43 - 45 are objected to because of the following informalities: the claims recite a two-vector system in the preamble, but only describe what the first vector comprises. There is no further mention of the second vector, hence, the claims are clumsy and confusing. Appropriate correction is required.

Claim 1 is objected to because of the following informalities: the claim recites a "first vector", strongly implying additional vectors. There is no further mention of an additional or second vector, hence, the claim is clumsy and confusing. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 2-3, 6-28, 31-36 and 38-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods and compositions comprising the AAV4 proteins set forth in SEQ ID NOs: 2, 4, 8, 9, 10, 11, 16 and 18, does not reasonably provide enablement for the claimed variants thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 2-3, 6-28, 30-36 and 38-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

While the written description and enablement requirements are separate and generally separable requirements, the instant application fails to meet either requirement for essentially the same reasons, as set forth below.

Applicants claim vectors and methods of using the vectors comprising the AAV proteins set forth in SEQ ID NOs: 2, 4, 8, 9, 10, 11, 16 and 18 or variants thereof based upon % homology. Applicants disclose a single amino acid sequence for each SEQ ID NO:. The claims read on a broad genus of potential vectors and methods comprising different and various amino acid sequences, such as any sequence that with 90% - 99% homology to SEQ ID NO: 4 (e.g. claim 2, a VP1 capsid protein), 95% homology to SEQ ID NOs: 2, 8, 9, 10, 11 (claims 17-25, Rep proteins), or 98% homology to SEQ ID NOs: 16 or 18 (claims 34-36, VP2 capsid proteins).

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The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention. The court and the Board have repeatedly held (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a biological sequence requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the sequence itself. It is not sufficient to define a protein solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any protein with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid or protein, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the protein has been isolated. Thus, claiming all proteins that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived.

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In terms of the structural requirements of the claimed proteins, the claims recite an arbitrary structural relationship between the claimed protein sequence(s) and the single disclosed species of amino acid sequences for each respective SEQ ID NO based upon a percent homology value. While one of skill in the art can readily envision numerable species of amino acid sequences that are at least a given % identity to a reference sequence, one cannot envision which of these also encode a polypeptide with a specified activity or be useful as required by this statute. The fact remains that the actual protein with a particular activity, or the actual amino acid sequences of such a protein, cannot be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a synthetic polypeptide with 90% identity to SEQ ID NO: 4, he would be no more able to say whether it encoded an AAV4 VP1 capsid protein than if the polypeptide was only 10% identical to SEQ ID NO: 4. Nor would he be able to say whether the sequence existed in nature.

In the instant case, applicants only disclose the actual amino acid sequences of the SEQ ID NOs recited in the claims. Neither applicants nor the prior art disclose other AAV4 capsid or rep protein sequences within the claim limitations, let alone ones that would be functional and therefore useful. Applicants are claiming variants of SEQ ID NOs: 2, 4, 8, 9, 10, 11, 16 and 18 by function and/or homology only, without a correlation between structure and function. Applicants provide no disclosure of what structural feature(s) of the instantly disclosed AAV4 rep and cap proteins are responsible for the observed functional properties as a vector system.

The specification does not provide any information on what amino acid residues are necessary and sufficient for the disclosed, necessary properties of the claimed AAV4 capsid and

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rep proteins, such as viral particle formation, infectivity, integration, etc. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a variant polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there were no other examples of functional AAV4 capsid or rep proteins known that have the claimed structural homology with SEQ ID NO: 4 (for example), it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. The comparison of SEQ ID NO: 4 to other AAV capsid proteins is of record. However, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo et al, 1994). Rudinger (in Peptide Hormones, 1976) discloses that even for peptide hormones, which are much smaller than the instant AAV4 proteins, one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in “case to case painstaking experimental study” to determine active variants (see page 7). Consequently, excessive trial and error experimentation would have been required to identify the necessary AAV4 capsid and rep derivatives since the amino acid sequence of such polypeptides could not be predicted - even were the activity known.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable

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factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other sequences embraced by the claim. This is the case here, where specification discloses only one putative functional amino acid sequence for each claimed SEQ ID NO, (e.g. SEQ ID NO: 4), and provides no guidance on determining which polypeptide variants of the claimed SEQ ID NO would have be functional AAV4 capsid or rep proteins.

To put the situation in perspective, the number of possible amino acid sequences of 734 amino acids in length (SEQ ID NO: 4 is 734) is 20^{700} (approx. 10^{910}). The number of possible amino acid sequences that are of a given % identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following expansion formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \dots + X^{n-1}L(L-1)(L-2)\dots(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)\dots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is

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the maximum number of residues that can be substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids). The n^{th} term of the expansion can be rewritten as:

$$X^n \cdot \frac{L!}{n! (L-(n-1))!}$$

For a 734-residue amino acid sequence that is at least 90% identical to a reference sequence of 734 amino acids, e.g. SEQ ID NO: 4, the number of possible sequences having 72 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 1.5×10^{190} , whereas the number of possible sequences having 73 amino acid substitutions relative to the reference (the final term of the formula) is approximately 3×10^{192} . So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. Even claiming 99% identity does little to realistically improve the situation, as the same analysis with SEQ ID NO: 4 using 99% homology (i.e. 7 substitutions) yields 2.3×10^{22} possible variants. Also, as the number of permitted substitutions increases the number of possible variant sequences increases geometrically. In a genus of polypeptides that are at least 90% identical to a reference, nearly all will be exactly 90% identical. While limiting the scope of potential sequences to those that are at least 90 or 99% identical to a reference, for example, greatly reduces the number of potential sequences to test, it does not do so in any meaningful way.

Response to Arguments

Applicant's arguments filed 9/29/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) the Examiner has misapplied case law, specifically the *Fiddes v. Baird* and *Lilly* decisions; 2) the BPAI has consistently reversed written

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description rejections based upon percent homology in the claims; 3) the misapplication of case law incorrectly alleges that a number of species has not been disclosed, all that is required is for the written description requirement is to identify the metes and bounds of the claims; 4) the written description requirement can be met without reciting a function, as set forth in the USPTO Training Materials; 5) the skilled artisan could have used knowledge in the prior art to identify conserved regions within VP1, for example; 6) the rejection relies upon evidence wherein large inactivating mutations (deletions, insertions) within VP1 or VP3 where intentional, and is not indicative of more subtle mutants encompassed by the claims; 7) the rejection overlooks the conserved nature of the AAV4 and AAV2 VP3 proteins, and that the teachings of Wu et al makes substitutions predictable; 8) the specification sets forth methods to screen for functional variants, which are routine in the art when used to test multiple mutations; 9) whether experimentation is undue is a function of identifying a single variant, not an almanac of all the AAV4 mutants encompassed by the claims; 10) the information in the art provides means to make variants above 70% homology, and the rejection has not provided any scientific or legal reasoning to refute this.

Regarding 1) and 3), the facts of these cases fit the instant rejection for reasons of record, even though the particulars (e.g. the particular protein or DNA sequence claimed) may differ. Essentially, the instant claims are so-called "reach-through" claims, attempting to claim subject matter not specifically disclosed. This is what essentially appears in the *Fiddes v. Baird* and *Lilly* decisions, i.e. an attempt to claim unknown subject matter (human sequences) only by homology to what is actually disclosed (rat or bovine sequences). Merely naming a protein sequence that may or may not exist, or may or may not have the necessary function, is not in

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compliance with the provisions of 35 USC 112 1st ¶ for reasons of record. According to applicants logic, merely claiming "A perpetual motion machine" would be all that is necessary to provide written description for the claimed machine. The metes and bounds of the claims is covered under 35 USC 112 2nd ¶.

Regarding 2), each application is judged on its own merits. The applications cited by applicants present no binding precedent by the BPAI. The particulars of the instant application and rejection have not been before the BPAI, hence, it is premature to argue what the BPAI may do in this instance. There appears to be nothing in the cases cited pertaining to the enablement rejection, nor how to make and test 3×10^{192} possible protein variants as encompassed by the instant claims. Finally, none of the references or BPAI decisions relied upon have been provided, hence, whatever information that might lie within has not been considered.

Regarding 4), even if this is held to be true, it does not teach how to make and use, i.e. enable, such a incomprehensibly large genus of potential protein variants as set forth above. Furthermore, the Guidelines are not rule making and are not binding. Such Guidelines do not take into account the reasoning set forth above. Finally, it is noted that several claims do recite functions (e.g. claims 43-45).

Regarding 5), this is not disputed. However, the claims are not limited to substitutions or variants within the conserved regions, and as set forth above, even minor changes in conserved amino acids can abrogate protein function. It is impossible to tell beforehand what effects such substitutions or variations will have on the protein, hence the unpredictable nature of making and using such variants.

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Regarding 6), the instant rejection does not rely upon these references or teachings.

Indeed, the case can be (and is) made using only substitution mutations alone, the very type of subtle mutations argued by applicants to be used by the skilled artisan when designing AAV4 mutations to preserve functionality.

Regarding 7), again, the claims are not limited to substitutions in conserved residues or domains, nor is the variation of such residues limited to only a few related amino acids (the premise of Wu et al and applicants analysis of the conservation between the AAV2 and AAV4 VP3 protein). Wu et al presents no experimental evidence for the functional substitution of such amino acids, only computer models. Wu et al leave the skilled artisan to then perform the experiments to find out which variants will actually work. Wu et al is silent regarding substitution mutation of AAV4 proteins, and there is no mention of the VP1 protein in applicants analysis. Applicants only offer an opinion that changing up to 55% of the amino acids in AAV4 VP3 to those suggested by Wu et al would be predictable. This is unsupported by any facts or evidence. "Argument of counsel cannot take the place of evidence lacking in the record." *In re Scarbrough*, 182 USPQ 298, 302 (CCPA 1974).

Regarding 8), asserting that the skilled artisan must prepare and discover what applicants have not disclosed by using a method set forth in the specification is not considered to meet the requirements of this statute for the reasons set forth above. Such experimentation is deemed undue: applicants have not taught how to make and use such a broad genus of substitution variants embraced by claim 45, for example (2.3×10^{22}), let alone those embraced by claim 2 (3×10^{192}).

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Regarding 9), the claims are much broader than a single variant for reasons set forth above. Applicants do not explain why the claims do not have to be enabled for their full scope, which is a requirement of U.S. patent law (MPEP 2164.01(a) and 2164.08). The analysis of the claimed scope above stands, and thus the specification must teach how to make and use a scope that is commensurate with the claims. An almanac of all the possible variants is within the claimed scope for reasons set forth above, and includes, even at 99% homology, 2.3×10^{22} variants. The instant specification provides no guidance or working examples for how to create and test such a large number of variants, let alone such a process wherein the experimentation is undue.

Regarding 10), the cited reference (Tian et al) is from 2003, and cannot enable an application seeking a filing date of 1996. Extensive scientific, mathematical, and legal reasoning is provided above. Applicants in turn offer no specific reasoning or evidence as to how to make and test such an incredibly large genus of variant proteins as instantly claimed (e.g. the 3×10^{192} variants of claim 2). Rather, applicants rely upon opinion and continue to insist that the claimed scope is much more narrow than a strict analysis of the claimed scope reveals.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 6-28, 38, 39, 41 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 3 recites the limitation "the second vector" in line 1. There is insufficient antecedent basis for this limitation in the claim. This rejection affects all dependent claims.

Conclusion

Claim 30 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHAEL BURKHART whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhardt/
Primary Examiner, Art Unit 1633